### 1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

**SCHEDULING STATUS**

**S3**

## 1 NAME OF THE MEDICINE

**SARTOC-CO 50/12,5 film-coated tablets**

**SARTOC CO 100/25 mg film-coated tablets**

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet of SARTOC-CO 50/12,5 contains 50 mg losartan potassium and 12,5 mg hydrochlorothiazide.

Contains sugar: Mannitol 51,20 mg

Each film-coated tablet of SARTOC CO 100/25 mg contains 100 mg losartan potassium and 25 mg hydrochlorothiazide.

Contains sugar: Mannitol 102,40 mg

For full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Film-coated tablets

SARTOC-CO 50/12,5: Yellow, round, biconvex, film-coated tablet. Tablet might be embossed with “A 55” on one side.

SARTOC CO 100/25 mg: Pale yellow, round, film-coated tablets.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

SARTOC-CO 50/12,5 and SARTOC CO 100/25 mg are indicated for the treatment of hypertension in patients stabilised on the same dose of each individual medicine.

### 4.2 Posology and method of administration

**Posology**

*Adults:* The usual starting dose of SARTOC-CO 50/12,5 is one tablet daily.

The maximum dose is one tablet of SARTOC CO 100/25 mg once daily.

For patients who do not respond adequately to SARTOC-CO 50/12,5, the dosage may be increased to one SARTOC-CO 100/25 mg tablet once daily. No initial dosage adjustment is required in elderly patients.

The maximal antihypertensive effect is attained within 3 weeks. SARTOC-CO may be administered in combination with other antihypertensive medicines such as calcium channel blockers and beta-blockers.

SARTOC-CO may be taken with food or on an empty stomach.
SARTOC-CO should not be initiated in patients who are intravascularly volume-depleted e.g. those patients on high-dose diuretics.

**Special populations**

*Elderly population*

SARTOC CO 100/25 mg should not be used as initial therapy in elderly patients.

*Renal impairment*

SARTOC-CO is not recommended for patients with severe renal impairment (see sections 4.3 and 4.4).

*Hepatic impairment*

SARTOC-CO is not recommended for patients with hepatic impairment (see sections 4.3 and 4.4).

**Paediatric population**

The safety and efficacy of SARTOC-CO in children has not been established.

**Method of administration**

For oral administration.

## 4.3. Contraindications

SARTOC-CO is contraindicated in:

- Patients with hypersensitivity to losartan potassium, hydrochlorothiazide, sulphonamide-derived medicines or to any of the excipients in SARTOC-CO.
- Patients with a history of angioedema related to previous therapy with ACE inhibitors or ARBs: These patients must never again be given these medicines.
- Patients with hereditary or idiopathic angioedema.
- Patients with hypertrophic obstructive cardiomyopathy (HOCM).

- Patients with moderate to severe renal function impairment (creatinine clearance less than 30 ml/min) and anuria.
- Patients with bilateral renal artery stenosis.
- Patients with renal artery stenosis in patients with a single kidney.
- Patients with aortic stenosis.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.5).
- Concomitant use with fluoroquinolones with ACE inhibitors/angiotensin receptor blockers, in patients with moderate to severe renal impairment (Creatine Clearance < 30 ml/min) and in elderly patients.
- Patients with porphyria.
- Patients with Addison's disease.
- Concomitant therapy with lithium. Administration with SARTOC-CO may lead to toxic blood concentrations of lithium (see section 4.5).
- Patients with severe hepatic function impairment, cholestasis and biliary obstructive disorders as increased plasma concentrations may occur. SARTOC-CO are not recommended since dose titration with losartan is needed.
- Therapy resistant hypokalaemia or hypercalcaemia.
- Refractory hyponatraemia.
- Symptomatic hyperuricemia/gout.
- Concomitant use with aliskiren-containing medicines in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1,73 $m^2$) (see section 4.4).
- Patients with a history of previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and lip.
- Paediatric use - The safety and efficacy of SARTOC-CO in paediatric patients has not been established.

- Pregnancy and lactation (see section 4.6).

## 4.4. Special warnings and precautions for use

**Pregnancy**

Should a woman become pregnant while receiving SARTOC-CO, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see sections 4.3 and 4.6).

Pregnant women should be informed of the potential hazards to the foetus and must not take SARTOC-CO during pregnancy (see section 4.3). Patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with SARTOC-CO should be stopped immediately and if appropriate, alternative therapy should be started. Foetal exposure to ACE inhibitors during the first trimester of pregnancy has been reported to be associated with an increased risk of malformations of the cardiovascular (atrial and/or ventricular septal defect, pulmonic stenosis, patent ductus arteriosus) and central nervous system (microcephaly, spina bifida) and of kidney malformations.

SARTOC-CO passes through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms. Oligohydramnios as well as hypotension, oliguria and anuria in new-borns, have been reported after administration of SARTOC-CO during the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur (see section 4.3).

*Hypersensitivity reactions*

Hypersensitivity reactions to hydrochlorothiazide, as in SARTOC-CO, may occur in

patients with or without a history of allergy or bronchial asthma.

*Angioedema*

Patients with a history of angioedema (swelling of the face, lips, throat, and/or tongue) should be closely monitored (see section 4.8).

*Renal impairment*

The area under the curve (AUC) may be increased by approximately 50 % in patients with moderate to severe renal function impairment. In patients whose renal function is dependent on the renin-angiotensin system, a risk of severe arterial hypotension, and (often acute) renal impairment especially those with congestive heart failure, there may be a risk of induced renal failure.

SARTOC-CO is not recommended for patients with severe renal impairment (see sections 4.2 and 4.3).

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function, including renal failure, have been reported (in particular, in patients whose renal function is dependent on the renin-angiotensin aldosterone system, such as those with severe cardiac insufficiency or pre-existing renal dysfunction).

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. Therefore, the plasma concentrations of potassium and creatinine clearance values should be closely monitored; especially patients with heart failure and a creatinine clearance between 30 to 50 ml/min.

Other medicines that affect the renin-angiotensin system may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, these changes in renal function may be reversible upon discontinuation of

therapy (see section 4.3). While not confirmed, this potentially may occur with ARBs. Losartan, as in SARTOC-CO, is contraindicated in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney (see section 4.3).

*Fluoroquinolones*

Concomitant use of fluoroquinolones and SARTOC-CO may precipitate acute kidney injury (AKI) in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3). Renal function should be assessed before initiating treatment, and monitored during treatment, with fluoroquinolones or SARTOC-CO whether used separately and/or concomitantly.

*Renal transplantation*

There is no experience in patients with recent kidney transplantation.

*Electrolyte imbalances*

The condition may be exacerbated. The correction of electrolyte imbalance prior to administration of SARTOC-CO is recommended.

SARTOC-CO should be used with caution in patients who are sodium or volume-depleted (e.g. those who have received high-dose diuretics). Symptomatic hypotension may occur following the initiation of therapy with SARTOC-CO. Sodium or volume-depletion should be corrected before initiating therapy (see section 4.2).

Patients should be observed for clinical signs of fluid or electrolyte imbalance, e.g. volume depletion, hyponatraemia, hyperchloremic alkalosis, hypomagnesemia or hypokalaemia which may occur during intercurrent diarrhoea or vomiting. Periodic determination of serum electrolytes should be performed at appropriate intervals in such patients.

Dilutional hyponatraemia may occur in oedematous patients in hot weather.

The concomitant use of potassium-sparing diuretics, potassium supplements and potassium containing salt substitutes with SARTOC-CO is contraindicated (see sections 4.3 and 4.5).

*Hyperuricemia or gout*

The condition may be exacerbated by hydrochlorothiazide, as in SARTOC-CO. Losartan, as in SARTOC-CO, however, decreases uric acid which may attenuate the diuretic-induced hyperuricemia.

*Systemic lupus erythematosus*

Hydrochlorothiazide, as in SARTOC-CO, may exacerbate or activate systemic lupus erythematosus.

*Non-melanoma skin cancer*

An increased risk of non-melanoma skin cancer (NMSC) (basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)) with increasing cumulative dose of hydrochlorothiazide (HCTZ), as in SARTOC-CO, exposure has been observed in two epidemiological studies. Photosensitising actions of hydrochlorothiazide, as in SARTOC-CO, could act as a possible mechanism for NMSC.

Patients taking hydrochlorothiazide, as in SARTOC-CO, should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients to minimise the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. SARTOC-CO should

not be used by patients who have had previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and/or lip (see section 4.3).

*Hepatic impairment*

SARTOC-CO is contraindicated in patients with severe hepatic impairment (see sections 4.2 and 4.3).

Plasma concentrations of losartan, as in SARTOC-CO, are significantly increased in cirrhotic patients. SARTOC-CO should be used with caution in patients with a history of mild to moderate hepatic impairment. There is no therapeutic experience with losartan, as in SARTOC-CO, in patients with severe hepatic impairment.

Thiazides, such as hydrochlorothiazide, as in SARTOC-CO, should be used with caution in patients with impaired hepatic function or progressive liver disease, as it may cause intrahepatic cholestasis, and since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

*Hypotension and intravascular volume depletion*

In patients who are intravascularly sodium and/or volume-depleted (e.g. those treated with high-dose diuretics, patients with dietary salt restriction, or patients with diarrhoea or vomiting), symptomatic hypotension may occur, especially after the first dose. These conditions should be corrected prior to administration of SARTOC-CO, or a lower starting dose should be used (see section 4.2 ). Periodic determination of serum electrolytes should be performed at appropriate intervals as in any patient receiving diuretics.

*Primary hyperaldosteronism*

Patients with primary aldosteronism generally will not respond to antihypertensive medicines acting through inhibition of the renin-angiotensin system. Therefore, the use of SARTOC-CO is not recommended.

*Diabetes mellitus*

Thiazide therapy, including hydrochlorothiazide, as in SARTOC-CO, may impair glucose tolerance and exacerbate diabetes mellitus. Dosage adjustment of antidiabetic medicines, including insulin, may be required (see section 4.5 ). Latent diabetes mellitus may manifest during thiazide therapy, including hydrochlorothiazide, as in SARTOC-CO.

*Hypercalcaemia*

Thiazides, including hydrochlorothiazide, as in SARTOC-CO, may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. SARTOC-CO should be discontinued before carrying out tests for parathyroid function.

*Cholesterol and triglycerides*

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy, including hydrochlorothiazide, as in SARTOC-CO.

*Coronary heart disease and cerebrovascular disease*

As with any antihypertensive medicines, excessive blood pressure decrease in patients with ischaemic cardiovascular and cerebrovascular disease could result in a myocardial infarction or stroke.

*Heart failure*

In patients with heart failure, with or without renal impairment, there is - as with other medicines acting on the reninangiotensin system - a risk of severe arterial hypotension, and (often acute) renal impairment.

*Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy*

As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

*Ethnic differences*

ACE inhibitors, including losartan, as in SARTOC-CO, and the other angiotensin antagonists are apparently less effective in lowering blood pressure in the black population than in the non-black population, possibly because of higher prevalence of low-renin states in the black hypertensive population.

*Dual blockade of the renin-angiotensin-aldosterone system (RAAS)*

There is evidence that the concomitant use of ACE-inhibitors, ARBs or aliskiren increases the risk of hypotension, hyperkalaemia, and decreases renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, ARBs or aliskiren is therefore not recommended (see sections 4.3 and 4.5). If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and ARBs should not be used concomitantly in patients with diabetic nephropathy.

*Choroidal effusion, acute myopia and secondary angle-closure glaucoma*

Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma.

*Concomitant use with lithium*

Concomitant administration of lithium with SARTOC-CO may lead to toxic blood concentrations of lithium (see sections 4.3 and 4.5).

*Excipients*

SARTOC-CO contains mannitol. Patients with the rare hereditary condition of mannitol intolerance should not take SARTOC-CO.

**Paediatric population**

Safety and efficacy in children had not been established (see section 4.3).

## 4.5. Interaction with other medicines and other forms of interaction

The antihypertensive effects of SARTOC-CO may be potentiated when taken together with other antihypertensive medicines.

**Losartan**

*Hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbitone, ketoconazole, and erythromycin:* No interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbitone, ketoconazole and erythromycin (see section 4.5, Hydrochlorothiazide below).

*Medicines affecting potassium levels:* An additive hyperkalaemic effect is possible with other medicines that block angiotensin II or its effects, potassium supplements, potassium-

sparing diuretics (e.g., spironolactone, triamterene, amiloride), salt substitutes containing potassium and other medicines that can cause hyperkalaemia. Co-administration is not advisable (see section 4.3).

*Rifampicin and fluconazole:* Rifampicin and fluconazole reduces levels of the active metabolite. The clinical consequences of these interactions have not been evaluated.

*Lithium:* Excretion may be reduced as with other medicines which affect the excretion of sodium (see sections 4.3 and 4.4).
Therefore, serum lithium levels should be monitored carefully if lithium salts are to be coadministered with angiotensin II receptor antagonists.

*Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors):* NSAIDs may alleviate the antihypertensive effect of losartan as in SARTOC-CO. Concomitant use of ARBs (such as losartan, as in SARTOC-CO) or diuretics (such as hydrochlorothiazide, as in SARTOC-CO) and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated, and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter. In some patients with compromised renal function who are being treated with NSAIDs, including selective cyclooxygenase-2 inhibitors, the co-administration of losartan, as in SARTOC-CO, may result in a further deterioration of renal function. These effects are usually reversible (see section 4.3 and 4.4).

*ACE-inhibitors, ARBs, aliskiren*: Dual blockade of the renin-angiotensin-aldosterone system (RAAS) through the combined use of ACE-inhibitors, ARBs or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia, and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting medicine. Do not co-administer aliskiren with SARTOC-CO in patients with diabetes. Avoid use of aliskiren with SARTOC-CO in patients with renal impairment (GFR < 60 ml/min) (see sections 4.3 and 4.4).

*ACE Inhibitors, Fluoroquinolones acute kidney injury (AKI).*
Concomitant use of SARTOC-CO and ACE inhibitors/angiotensin receptor blockers may precipitate acute kidney injury. The mechanisms of the possible interactions between the different classes of medicines, over and above different mechanisms of kidney damage is unknown (see sections 4.3 and 4.4).

Data indicated a greater than additive risk of AKI with co-prescribed fluoroquinolones and renin angiotensin blockers. High proportion of patients were at risk of AKI including ACE inhibitor adverse renal effects, however AKI did not occur until ciprofloxacin, a fluoroquinolone was added.

There is a 4,6-fold increased risk of AKI with concomitant use of ARBs and fluoroquinolones. However, the mechanism of the interaction is unclear.
*Hypotension inducing medicines* (e.g. tricyclic antidepressants, antipsychotics, baclofen, amifostine): Concomitant use with these medicines that lower blood pressure, as main or side effect, may increase the risk of hypotension.

**Hydrochlorothiazide**

*Alcohol, narcotics, antidepressants or barbiturates:* Concurrent use with hydrochlorothiazide, as in SARTOC-CO, may potentiate orthostatic hypotension.
*Antidiabetic medicines (oral medicines and insulin)*: Hydrochlorothiazide, as in SARTOC-CO, may increase blood glucose concentrations. Dosage adjustment of the antidiabetic medicine may be necessary. Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide, as in SARTOC-CO (see section 4.4).

*Cholestyramine or colestipol resins:* The absorption of hydrochlorothiazide, as in SARTOC-CO, may be reduced in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide, as in SARTOC-CO, and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively. SARTOC-CO should be administered at least one hour before taking cholestyramine or colestipol.

*Corticosteroids, amphotericin B (parenteral), stimulant laxatives, glycyrrhizin (found in liquorice) or ACTH:* Concurrent use with hydrochlorothiazide, as in SARTOC-CO, may aggravate electrolyte depletion, particularly hypokalaemia.

*Sympathomimetics (Pressor amines e.g. adrenaline)*: Concurrent use may decrease the response to sympathomimetic medicines but not sufficient to preclude their use.

*Neuromuscular blocking medicines or skeletal muscle relaxants (e.g. tubocurarine, pancuronium)*: Concurrent use of hydrochlorothiazide, as in SARTOC-CO, may enhance the blockade of non-depolarising neuromuscular blocking medicines.
*Lithium:* Concurrent use of hydrochlorothiazide, as in SARTOC-CO, may reduce the renal

clearance of lithium and increase the risk of lithium toxicity. Concomitant use is not recommended (see section 4.3).

*Medicines used in the treatment of gout (e.g. probenecid, sulfinpyrazone and allopurinol):* Dosage adjustment of uricosuric medicines may be necessary since hydrochlorothiazide, as in SARTOC-CO, may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of a thiazide, such as hydrochlorothiazide, as in SARTOC-CO, may increase the incidence of hypersensitivity reactions to allopurinol.

*Anticholinergic medicines (e.g. atropine, biperiden):* Increase of the bioavailability to thiazide-type diuretics such as hydrochlorothiazide, as in SARTOC-CO, by decreasing gastrointestinal motility and stomach emptying rate.

*Cytotoxic medicines (e.g. cyclophosphamide, methotrexate):* Thiazides such as hydrochlorothiazide, as in SARTOC-CO, may reduce the renal excretion of cytotoxic medicines and potentiate their myelosuppressive effects.
*Salicylates:* In case of high dosages of salicylates hydrochlorothiazide, as in SARTOC-CO, may enhance the toxic effect of the salicylates on the central nervous system.
*Methyldopa*: Haemolytic anaemia may occur with concomitant use of hydrochlorothiazide, as in SARTOC-CO, and methyldopa.
*Ciclosporin:* Concomitant treatment with ciclosporin may increase the risk of hyperuricemia and gout-type complications.

*Digitalis glycosides:* Hypokalaemia or hypomagnesaemia, induced by thiazides such as hydrochlorothiazide, as in SARTOC-CO, may favour the onset of digitalis-induced cardiac dysrhythmias.

*Medicines affected by serum potassium disturbances*: Periodic monitoring of serum potassium and ECG is recommended when SARTOC-CO is administered with medicines affected by serum potassium disturbances (e.g. digitalis glycosides and antidysrhythmics) and with the following torsades de pointes (ventricular tachycardia)-inducing medicines (including some antidysrhythmics), hypokalaemia being a predisposing factor to torsades de pointes (ventricular tachycardia):

- Class IA antidysrhythmics (e.g. quinidine, hydroquinidine, disopyramide).
- Class III antidysrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide).
- Some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol).
- Others (e.g. bepridil, cisapride, diphemanil, erythromycin IV, halofantrin, mizolastin, pentamidine, terfenadine, vincamine IV).

*Calcium salts*: Hydrochlorothiazide, as in SARTOC-CO, may increase serum calcium levels due to decreased excretion. If calcium supplements must be prescribed, serum calcium levels should be monitored, and calcium dosage should be adjusted accordingly.

*Laboratory test interactions:* Because of their effects on calcium metabolism, thiazides such as hydrochlorothiazide, as in SARTOC-CO, may interfere with tests for parathyroid function (see section 4.4).

*Carbamazepine*: There is a risk of symptomatic hyponatraemia. Clinical and biological monitoring is required.

*Iodine contrast media:* In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of the iodine medicine. Patients should be rehydrated before the administration.

*Non-steroidal anti-inflammatory drugs (NSAIDs):* NSAIDs may reduce the diuretic, natriuretic and antihypertensive effects of diuretics.

## 4.6. Fertility, pregnancy and lactation

**Women of childbearing potential**

Women of childbearing age should ensure adequate contraception.

**Pregnancy**

The safety of SARTOC-CO in pregnancy and lactation has not been established (see section 4.3). Should be discontinued if pregnancy is planned or confirmed.

*Losartan as in SARTOC-CO*

Medicines affecting the renin-angiotensin system, such as losartan, as in SARTOC-CO, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women.

ARBs, including losartan, as in SARTOC-CO, should not be initiated during pregnancy. Patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with SARTOC-CO should be stopped immediately, and, if appropriate, alternative therapy should be started.

SARTOC-CO is contraindicated during pregnancy (see section 4.3). Data regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however, a small increase in risk cannot be excluded.

Exposure to losartan, as in SARTOC-CO, during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, anuria, oligohydramnios (associated with foetal lung hypoplasia), skull ossification retardation, skull hypoplasia) and neonatal toxicity (renal failure, hypotension, hyperkalaemia and death). Should exposure to SARTOC-CO have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken SARTOC-CO should be closely observed for hypotension (see section 4.3).

*Hydrochlorothiazide as in SARTOC-CO*

There is limited experience with hydrochlorothiazide, as in SARTOC-CO, during pregnancy, especially during the first trimester.
Hydrochlorothiazide, as in SARTOC-CO, crosses the placenta barrier and appears in cord blood. Based on the pharmacological mechanism of action of hydrochlorothiazide, as in SARTOC-CO, its use during second and third trimesters may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.
Hydrochlorothiazide, as in SARTOC-CO, should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.
Hydrochlorothiazide, as in SARTOC-CO, should not be used for essential hypertension in pregnant women. Foetal or neonatal jaundice has been reported.

**Breastfeeding**

SARTOC-CO is contraindicated in lactation (see section 4.3 ).

*Losartan as in SARTOC-CO*

Because no information is available regarding the use of SARTOC-CO during breastfeeding, SARTOC-CO is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a new-born or pre-term infant.

*Hydrochlorothiazide*

Hydrochlorothiazide, as in SARTOC-CO, is excreted in human milk in small amounts. SARTOC-CO in high doses causing intense diuresis can inhibit the milk production. The use of SARTOC-CO during breastfeeding is not recommended.

**Fertility**

There are insufficient fertility data available to indicate whether SARTOC-CO has any effect on fertility.

## 4.7. Effects on ability to drive and use machines

SARTOC-CO has moderate influence on the ability to drive and use machines since adverse reactions such as dizziness and blurred vision have been reported in patients receiving SARTOC-CO (see section 4.8).

## 4.8. Undesirable effects

*Tabulated list of adverse reactions for SARTOC-CO*

| System organ class | Frequent | Less Frequent |
|---|---|---|
| **Metabolism and nutrition disorders** | | Hyperkalaemia, electrolyte imbalance including hyponatraemia and hypokalaemia |

| | | |
|---|---|---|
| **Nervous system disorders** | Dizziness | |
| **Hepato-biliary disorders** | | Hepatitis |
| **General disorders and administrative site conditions** | Asthenia, fatigue | |
| **Investigations** | | Elevation of alanine amino transferase (ALT) |

*Tabulated list of adverse reactions for Losartan potassium*

| **System organ class** | **Frequent** | **Less Frequent** |
|---|---|---|
| **Infections and infestations** | Upper respiratory infection | Urinary tract infection, bronchitis |
| **Blood and the lymphatic system disorders** | Anaemia, haemolysis | Thrombocytopenia |
| **Immune system disorders** | | Hypersensitivity, anaphylactic reactions |
| **Metabolism and nutrition disorders** | Hyperkalaemia, hypoglycaemia | Anorexia, gout, hyponatraemia |
| **Psychiatric disorders** | Insomnia | Anxiety, anxiety disorder, panic disorder, confusion, depression, abnormal dreams, sleep disorder, somnolence, memory impairment |
| **Nervous system disorders** | Headache, dizziness | Migraine, nervousness, paraesthesia, peripheral neuropathy, tremor, syncope, vertigo, dysgeusia |

| | | |
|---|---|---|
| **Eye disorders** | | Blurred vision, burning/stinging in the eye, conjunctivitis, decrease in visual acuity |
| **Ear and labyrinth disorders** | | Tinnitus |
| **Cardiac disorders** | Chest pain, palpitations, tachycardia | Angina pectoris, grade II-AV block, cerebrovascular event, myocardial infarction, dysrhythmias (atrial fibrillations, sinus bradycardia, ventricular tachycardia, ventricular fibrillation) |
| **Vascular disorders** | | Orthostatic hypotension (dose-related), oedema, hypotension, vasculitis |
| **Respiratory, thoracic and mediastinal disorders** | Cough, nasal congestion, sinusitis, sinus disorder, pharyngitis | Pharyngeal discomfort, laryngitis, dyspnoea, epistaxis, rhinitis, respiratory congestion |
| **Gastrointestinal disorders** | Abdominal pain, diarrhoea, dyspepsia, nausea | Constipation, dental pain, dry mouth, flatulence, gastritis, vomiting, obstipation, pancreatitis |
| **Hepato-biliary disorders** | | Liver function abnormalities |

| | | |
|---|---|---|
| **Skin and subcutaneous tissue disorders** | | Rash, urticaria, Henoch-Schönlein purpura, angioedema (involving swelling larynx and glottis causing airway obstruction, swelling of the face, lips, pharynx and/or tongue; angioedema had been reported in connection with the administration of other medicines, including ACE inhibitors), alopecia, dermatitis, dry skin, erythema, flushing, photosensitivity, pruritus, sweating, ecchymosis, erythroderma |
| **Musculoskeletal, connective tissue and bone disorders** | Muscle cramps or pain (myalgia), back pain, leg pain, arm pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, coxalgia, fibromyalgia, muscle weakness | Rhabdomyolysis |
| **Renal and urinary disorders** | Renal impairment, renal failure | Nocturia, urinary frequency |
| **Reproductive system and breast disorders** | | Decreased libido, erectile dysfunction/impotence |
| **General disorders and administrative site conditions** | Asthenia, fatigue, oedema/swelling | Sternalgia, facial oedema, fever, flu-like symptoms, malaise |

| | | |
|---|---|---|
| **Investigations** | Mild reduction of haematocrit and haemoglobin | Elevations of alanine amino transferase (ALT), mild increase in urea and creatinine serum levels, increase in hepatic enzymes and bilirubin |

*Tabulated list of adverse reactions for Hydrochlorothiazide*

| System organ class | Frequent | Less Frequent | Frequency unknown |
|---|---|---|---|
| **Infections and infestations** | | Sialadenitis | |
| **Neoplasms benign, malignant and unspecified (incl. cysts and polyps)** | | Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma) | |
| **Blood and lymphatic system disorders** | | Agranulocytosis, leukopenia, thrombocytopenia, aplastic anaemia, haemolytic anaemia | |
| **Immune system disorders** | | Respiratory distress including pneumonitis and pulmonary oedema, anaphylactic reactions | |
| **Metabolism and nutrition disorders** | Electrolyte disturbances, hyperkalaemia | Hyperuricemia, hyperglycaemia, anorexia, hypokalaemia, hyponatraemia | |
| **Psychiatric disorders** | | Insomnia, restlessness | |
| **Nervous system disorders** | Cephalalgia | Vertigo, paraesthesias, headache, dizziness | |
| **Eye disorders** | | Xanthopsia, transient blurred vision | Choroidal effusion |
| **Vascular disorders** | | Hypotension (including orthostatic hypotension), necrotising angiitis (vasculitis, cutaneous vasculitis) | |
| **Respiratory, thoracic and mediastinal disorders** | | Respiratory distress including pneumonitis and pulmonary oedema | |

| | | | |
|---|---|---|---|
| **Gastrointestinal disorders** | | Gastric irritation, nausea, vomiting, cramping/spasms, diarrhoea, constipation, pancreatitis | |
| **Hepato-biliary disorders** | | Cholecystitis, icterus (intrahepatic cholestasis jaundice) | |
| **Skin and subcutaneous tissue disorders** | | Skin rash, urticaria, purpura, photosensitivity, toxic epidermal necrolysis (TEN), Cutaneous lupus erythematosus | |
| **Musculoskeletal, connective tissue and bone disorders** | | Muscle spasm, muscle cramps | |
| **Renal and urinary disorders** | | Renal dysfunction, interstitial nephritis, renal failure, glycosuria | |
| ***General disorders and administrative site conditions*** | | Fever, weakness | |

*Description of selected adverse reactions*

Cases of choroidal effusion with visual field defect have been reported after the use of thiazide and thiazide-like diuretics.

*Reporting of suspected adverse reactions*

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to:

**SAHPRA:** https://www.sahpra.org.za/health-products-vigilance/

**Aspen Pharmacare:**

**E-mail:** Drugsafety@aspenpharma.com

**Tel:** 0800 118 088

## 4.9. Overdose

### Symptoms

### Losartan

Limited data are available regarding overdose. The most likely symptoms of overdose include hypotension and tachycardia. Bradycardia may occur following parasympathetic (vagal) stimulation (see section 4.8 ). Neither SARTOC-CO nor the active metabolites can be removed by haemodialysis.

### Hydrochlorothiazide

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digitalis has been administered, hypokalaemia may accentuate cardiac dysrhythmias.

### Treatment

No specific information is available on the treatment of overdose with SARTOC-CO.

Treatment of SARTOC-CO overdose is symptomatic and supportive.

Therapy with SARTOC-CO should be discontinued and the patient should be observed closely.

SARTOC-CO overdose should be treated by immediate evacuation of the stomach, by induction of emesis if ingestion is recent, followed by supportive, symptomatic treatment and monitoring of electrolyte or serum concentrations and renal function. Suggested measures include correction of dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures. The degree to which hydrochlorothiazide, as in

SARTOC-CO, is removed by haemodialysis has not been established.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. Pharmacodynamic properties

Catergory and Class: Vascular medicines

Pharmacotherapeutic group: A 7.1.3 Other hypotensives

ATC code: C09DA01

*Mechanism of Action*

SARTOC-CO 50/12,5 and SARTOC CO 100/25 mg contains a combination of losartan, an angiotensin ll receptor blocker (ARB) and hydrochlorothiazide, a thiazide diuretic.

**Losartan**

Losartan is a synthetic, orally active medicine which has a high determinant of the pathophysiology of hypertension. Angiotensin II binds to the $AT_1$ receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth muscle cell proliferation. Losartan and its pharmacologically active carboxylic acid metabolite (E-3174) inhibits the biological effects of angiotensin ll regardless of the source of synthesis. Losartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin ll by inhibiting the binding of angiotensin ll to the $AT_1$ receptor. Losartan does not bind to or block other hormone receptors or ion channels important in cardiovascular regulation. Losartan does not inhibit angiotensin converting enzyme (ACE) (kininase II), the enzyme that degrades bradykinin.

**Hydrochlorothiazide**

Hydrochlorothiazide increases urinary excretion of sodium, chloride (in approximately equivalent amounts) and water by inhibiting sodium reabsorption in the early distal tubules. Hydrochlorothiazide initially decreases extracellular volume and cardiac output. However, the long-term hypotensive effect is maintained because of reduced vascular resistance. The diuretic effect of hydrochlorothiazide decreases plasma volume, resulting in increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, decreases in serum potassium, magnesium and bicarbonate. Since the renin-aldosterone link is mediated by angiotensin II, co-administration of losartan helps to reverse potassium loss associated with hydrochlorothiazide.
After oral use diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

**Losartan potassium and hydrochlorothiazide**

Hydrochlorothiazide enhances the antihypertensive effects of losartan (additive efficacy).

## 5.2. Pharmacokinetic properties

**Losartan**

**Absorption**

Losartan is well absorbed after oral administration with a bioavailability of approximately 33 %. It undergoes substantial first-pass metabolism by the cytochrome P450 system forming an active carboxylic acid metabolite and other inactive metabolites.
There is no clinically significant effect on the plasma concentration profile of losartan when losartan was administered with a standardised meal.
The time to peak concentration of the parent compound is 1 hour and that of the carboxylic acid metabolite is 3 to 4 hours.

**Distribution**

Losartan and its active metabolite are 99 % and more bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 litres.

**Biotransformation**

Biotransformation results in a major carboxylic acid metabolite that is 10 to 40 times more potent than the parent compound and is responsible for most of the pharmacological activity. About 14 % of an orally administered dose of losartan is converted to its active metabolite.

**Elimination**

Plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26 ml/min, respectively. When losartan potassium is administered orally, about 4 % of the dose is excreted unchanged in the urine, and about 6 % of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg. Following oral administration, plasma concentrations of losartan and its active metabolite decline poly-exponentially. The elimination half-life of losartan is approximately 2 hours while that of the active metabolite is approximately 6 to 9 hours. Faecal (biliary) excretion accounts for the elimination of 60 % of the dose and renal excretion for approximately 35 %. Neither losartan nor the metabolite can be removed by haemodialysis.

**Special populations**

**Hepatic impairment**

Plasma concentrations of losartan and its active metabolite are respectively 5-fold and 1,7-fold greater in patients with mild to moderate alcoholic cirrhosis of the liver.

**Hydrochlorothiazide**

**Absorption**

Hydrochlorothiazide is rapidly absorbed after oral administration.

**Distribution**

Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

**Biotransformation**

Hydrochlorothiazide is not metabolised and is almost totally eliminated via the kidneys, with only minute quantities eliminated in the bile.

**Elimination**

The plasma half-life has been reported to vary between 5,6 and 14,8 hours with the peak diuretic effect being observed after 4 hours. At least 61 % of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide is eliminated unchanged by the kidney.

**Losartan potassium and hydrochlorothiazide**

Hydrochlorothiazide 12,5 mg does not alter the pharmacokinetics of losartan 50 mg and vice versa.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. List of excipients

Hydroxypropyl cellulose, hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, povidone, propylene glycol, quinoline yellow aluminium lake, sodium starch glycollate, sorbic acid, sorbitan monooleate, starch maize, titanium dioxide, vanillin

### 6.2. Incompatibilities

Not applicable.

### 6.3. Shelf life

24 months

### 6.4. Special precautions for storage

Store at or below 25 °C.

Keep the blister strip in the unit carton until required for use.

Protect from light.

### 6.5. Nature and contents of container

SARTOC-CO 50/12,5

30 tablets are packed in a white opaque polyvinylchloride/polyethylene/polyvinylidene chloride blister strip sealed with an aluminium foil backing. The blister strips are packed into an outer cardboard unit carton together with a leaflet.

SARTOC CO 100/25 mg

30 tablets are packed in a white opaque polyvinylchloride/polyethylene/polyvinylidene chloride blister strip sealed with an aluminium foil backing. The blister strips are packed into an outer cardboard unit carton together with a leaflet.

Not all packs and pack sizes are necessarily marketed.

### 6.6. Special precautions for disposal

No special requirements.

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

## 8. REGISTRATION NUMBER

SARTOC-CO 50/12,5: 41/7.1.3/0956

SARTOC CO 100/25 mg: 42/7.1.3/0288

## 9. DATE OF FIRST AUTHORISATION

SARTOC-CO 50/12,5: 19 March 2010

SARTOC CO 100/25 mg: 05 August 2011

## 10. DATE OF REVISION OF TEXT

06 March 2023

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